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Review

What is the role for EEG after sleep deprivation in the diagnosis of epilepsy? Issues, controversies, and future directions

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ABSTRACT

In patients with a first seizure, the identification of early sensitive and specific biomarkers for formulating a diagnosis of epilepsy is fundamental. Sleep deprivation (SD) has long been used as a means of enhancing EEG sensitivity in the diagnostic process. However, huge methodological differences among the studies addressing this topic have led to highly variable results and often confusing assumptions. Here, we provide a detailed description of the correlations between SD and epilepsy, along with their putative mechanistic explanations derived from experimental studies in animals and humans. We also outline the clinical studies evaluating the role of SD EEG and discuss them critically in terms of: (a) study design and SD EEG methodology; (b) EEG sensitivity and specificity; (c) the role of drug-induced sleep EEG and EEG during spontaneously occurring sleep; and (d) the relevance of patient features, syndromes, and subsyndromes, as well as their correlations with neuroimaging details. Finally, we propose specific studies that might increase the role of SD EEG in the diagnosis and prognosis of epilepsy.

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1. Introduction

An epileptic seizure is the clinical manifestation of "abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). A single epileptic seizure occurs in up to 5% of the general population (Sander and Shorvon, 1996).

Epilepsy has been defined as "a chronic neurologic condition characterized by recurrent epileptic seizures" (Blume et al., 2001), and this definition implies the presence of at least two spontaneous seizures occurring more than 24 h apart (Hauser et al., 1991). A newer definition has been provided by an ad-hoc Commission of the International League Against Epilepsy (ILAE) (Fisher et al., 2005) and refers to epilepsy as a group of disorders, having in common "an abnormally increased predisposition to seizures". Besides the occurrence of at least one seizure, this requires the presence of an "enduring alteration in the brain" making seizures more likely to occur, so that "a single epileptic seizure due to an enduring epileptogenic abnormality would indicate epilepsy, and a single epileptic seizure in a normal brain would not" (Fisher et al., 2005).

The latter definition is the result of an ongoing debate among epileptologists, which stems from the need to set criteria for an early diagnosis. In epilepsy, an early diagnosis is fundamental, not only to prevent recurrent attacks, but also in light of the detrimental effects which seizures, especially if prolonged, have on the brain itself. On the other hand, prescribing antiepileptic drugs (AEDs) to a non-epileptic subject can also have unfavorable consequences. Prolonged AED treatment can impair cognitive performance, and sometimes has systemic side effects (especially the older AEDs—see, for instance, Perucca and Gilliam, 2012). In addition, the stigma still surrounding the diagnosis of epilepsy in many cultures often represents an additional burden for the patients.

Thus, early identification of sensitive and specific biomarkers is fundamental for the diagnosis of epilepsy, and was a priority in the previous Epilepsy Research Benchmarks (http://www.ninds.nih.gov/research/epilepsyweb/2007_benchmarks.htm), and in the latest 2014 version (http://www.ninds.nih.gov/research/epilepsyweb/2014benchmarks.htm) approved by the National Institute for Neurological Disorders and Stroke.

Despite innovation, there is still no biomarker available that distinguishes an epileptic seizure from other types of paroxysms, such as syncope, parasomnia, or psychogenic non-epileptic seizures (Cragar et al., 2002; McKeon et al., 2006). It is also impossible to measure "enduring predisposition" to seizures.

With respect to imaging techniques, [18F]fluorodeoxyglucose positron emission tomography is only used to identify the epileptic foci in selected patients, and is considered to be a tool with low specificity, despite the huge amount of data produced in the early 1990s (Kumar and Chugani, 2013a,b). The routine use of magnetic resonance imaging (MRI) has brought about substantial diagnostic advancements. High-field MRI scans have improved the diagnostic accuracy of focal epilepsy. In many cases that were previously classified as "cryptogenic", MRI provided a diagnosis. Functional MRI (fMRI) is used for the planning of epilepsy surgery to highlight functionally relevant areas which must not be resected (Sabsevitz et al., 2003). fMRI, however, is not useful for the diagnosis of epilepsy and cannot determine seizure proneness.

Electroencephalography (EEG) has been the most used diagnostic tool for epilepsy for many years. The onset, spreading, and termination of seizures occasionally can be monitored in this way. However, for most epilepsy patients with sporadic and unpredictable seizures, the main role of EEG is to pinpoint abnormalities during the interictal period. Interictal epileptiform discharges (IEDs) are considered to be manifestations of the hyperexcitability of the neuronal groups underlying the seizure onset. Several IED patterns have been characterized by intracranial EEG recordings during presurgical evaluations, and are likely to reflect distinct cellular phenomena (for an extensive review, see de Curtis et al., 2012). Those obtained during scalp EEG recordings are classically divided into spikes (or polyspikes), sharp waves, spike- (or polyspike-) and-wave, and spike-and-slow-wave complexes, and are assumed to occur far more frequently in patients with epilepsy than in healthy individuals (Chang et al., 2011). Ideally, if there is a clinical history of at least one clear epileptic seizure, it would be sufficient to make a diagnosis of epilepsy if IEDs are present on a routine EEG. By the same reasoning, a lack of IEDs would then be sufficient to rule out epilepsy. This opinion is widely held, even among some non-epileptologist neurologists. Unfortunately, up to 40% of patients suffering from clear recurrent epileptic seizures do not show IEDs during routine EEGs (Binnie and Prior, 1994), which is why efforts to improve the potential of EEGs to unveil IEDs have been made.

The role of sleep in modifying seizure threshold has been studied for decades. Soon after its inclusion in the clinical routine assessment of epilepsy patients, it was shown that sleep affected EEG "activations" in many of them. Shortly afterwards, sleep deprivation (SD) was proposed as a reliable tool to induce sleepiness and sleep during EEG recordings, thus increasing the incidence of IEDs. Nevertheless, its precise role in the diagnostic process of epilepsy has not been fully clarified after more than 40 years of use.

The precise value of an EEG performed after SD, with respect to sensitivity (i.e. making a diagnosis of epilepsy), specificity (i.e. ruling out epilepsy), and prognosis (i.e. predicting the recurrence of seizures), still remains a matter of debate. The following questions should therefore be addressed: (1) in a subject experiencing a suspected epileptic seizure and with a normal basal EEG, would the occurrence of IEDs on an SD EEG lead to the diagnosis of epilepsy? And (2) could the absence of IEDs in the same situation exclude this diagnosis?

Only if these questions were satisfactorily answered, could the precise potential of IEDs as an "epilepsy biomarker" during an SD EEG be declared. Identifying this role would be an achievement for some epilepsy subgroups as the term "epilepsy" includes a variety of diseases and/or syndromes which are often significantly different from one from another.

In all neurology practices and clinics, SD EEG is the most consistently used and easily accessible of the above-mentioned techniques: thus, its full elucidation as an essential diagnostic tool would be of paramount importance.

In this review, we detail the state-of-the-art knowledge of the specific role of SD EEG in the diagnosis of epilepsy as well as the current hypotheses on the pathophysiologic mechanisms which might explain this role. We emphasize how a considerable number of studies in the field show several methodological limitations with regard to design, inclusion criteria, and data analysis. On the whole, these limitations significantly hinder the formulation of conclusive remarks.

After considering the most relevant data in each report, we outline how an SD EEG repeatedly improved the sensitivity of the diagnosis of epilepsy and of the specific epilepsy syndromes (i.e. focal vs. generalized). This highlights the potential of SD to improve the appropriateness of AED prescription. Our analysis allows us to speculate about the planning of rigorous, but simple, studies which might address the unresolved issues. We discuss some future directions at the end of the paper, with the intention to raise debate about the actual value of SD EEG, which is too often underestimated.

2. Historical background on sleep–epilepsy interaction

The existence of a relationship between sleep and epilepsy was first hypothesized by Hippocrates and Aristotle, and subsequently remarked upon by Galen. These authors emphasized the frequency of nocturnal seizures and the importance of a good sleep hygiene

for epilepsy patients (reviewed in Temkin, 1994). In the late 1870s, at the beginning of the modern era of epileptology, William Richard Gowers speculated about the influence of the sleep–wake cycle on institutionalized epileptic patients. The subsequent introduction of a non-invasive recording of brain activity the EEG, by Hans Berger, brought those preliminary clinical observations into the field of neurophysiology (Cobb, 1969). In 1947, Gibbs and Gibbs described an increase in interictal epileptiform activity during sleep compared with wakefulness (Gibbs and Gibbs, 1947). This observation was confirmed in subsequent reports, and a specific role for the rapid-eye-movement/slow-wave sleep (REM/SWS) cycle was suggested, with seizures predominating during non-rapid-eye-movement (NREM) sleep and being suppressed during REM sleep (Billiard, 1982; Gloor et al., 1958). This pattern was initially verified for partial epilepsies, in which an increased risk of secondary generalization during NREM sleep was noted for partial seizures arising from the frontal (Janz, 1974) and temporal lobes (Billiard, 1982; Gloor et al., 1958). In 1973, Sato et al., demonstrated that absence-related 3-Hz spike-and-slow-wave complexes preferentially occurred during SWS, and were significantly abolished by REM sleep Sato et al. (1973).

Based on these clinical and EEG observations, a series of papers in the 1960s and 1970s investigated the role of SD in promoting epileptic seizures and facilitating IEDs. Janz (1962) described the effect of SD and alcohol consumption in grand mal patients, while observations of military personnel referred for tonic–clonic seizures confirmed the role of SD as a possible seizure trigger (Bennett, 1963; Gunderson et al., 1973). Rodin et al. (1962) deprived 16 healthy students of sleep for up to 120 h. Five of these students displayed high-voltage paroxysmal activity, similar to the paroxysms seen in patients with "convulsive disorders". This increased cerebral excitability appeared limited to the first 48 h of sleeplessness and, as reported by Rodin et al. (1962), the same subjects showed low thresholds for intravenous megimide.

Shortly after these reports, many epileptologists suggested that patients with suspected epileptic seizures and a normal or inconclusive routine EEG should undergo an SD EEG, to promote seizures and increase the likelihood of IEDs (Cobb, 1969). In parallel, the Advisory Group for Aerospace Research and Development stated that sleep-deprived individuals showing epileptiform EEG abnormalities had a low epilepsy threshold (Johnson and Naitoh, 1974). In spite of the methodological discrepancies among the studies, Naitoh and Dement (1975) officially identified SD as an activation method, and suggested that similar protocols should be used in all laboratories.

From the 1960s until now, many authors have also debated whether SD per se, sleep induction following SD, or simply a repeat EEG recording has a differential effect on the occurrence of interictal abnormalities (Veldhuizen et al., 1983). In the present review, the latter aspects are extensively addressed.

3. Experimental studies on the effects of SD on cortical excitability, EEG, and seizure susceptibility

Over the last 30 years, several studies on the effects of SD were conducted on experimental animals (especially rodents and cats), and most reports confirmed a strong influence of SD on the susceptibility to epileptiform discharges.

In the 1960s, Cohen and Dement first observed a significant reduction in the baseline threshold to electroconvulsive shock in REM-SD Wistar rats compared with non-SD controls (Cohen and Dement, 1965), and subsequently replicated these findings in cats (Cohen et al., 1967).

Several years later, Shouse and Sterman (1982) and Shouse (1988a) identified a relationship between sleep loss and the increase in seizure susceptibility in two feline epilepsy models, amygdala kindling (a model of focal limbic epileptogenicity) and systemic penicillin-induced seizures (a model of generalized seizures). These authors demonstrated that SD increased the amplitude of motor-evoked potentials in both models. However, it did not alter the pre-existing level of somatomotor cortical excitability, which was tightly dependent on the specific wakefulness or sleep stage (Shouse, 1988b, 1987).

Further studies conducted on rodent models do not show uniform results. Grahnstedt (1986) reported an increase in seizure susceptibility in amygdala-kindled Wistar rats after 58-h near-total SD, whereas a 54-h selective REM SD resulted in a delayed enhancement of seizure vulnerability, beginning 24 h after SD and persisting throughout the subsequent 72 h. The results in the near-total SD group were significantly undermined by the concomitant food and water deprivation, which acted as a potential confounding factor (Grahnstedt, 1986). A series of reports linked elective REM SD to a reduction in the threshold for nicotine-induced seizures in rats (Santos and Carlini, 1988) and for pentylenetetrazol-induced convulsions in mice (Vale and Leite, 1988). Similarly, Kumar and Raju (2001) reported a slight increase in afterdischarge threshold in amygdala-kindled rats after enhancing REM sleep with carbachol. Drinkenburg et al. (1995) induced a 12-h SD on a Wistar Albino Glaxo/Rij (WAG/Rij) rat strain, a model of congenital absence seizures. An increase in spike-and-wave discharges compared with baseline was recorded during only the first 4 h of SD, while the discharge index returned to baseline for the subsequent 8 h (Drinkenburg et al., 1995). Interestingly, there was a decrease in spike-and-wave discharges during the first hours of the post-deprivation recovery period. The authors speculated that both a stronger sleep propensity in the last part of the SD period and the sleep rebound during the recovery period could suppress epileptiform discharges (Drinkenburg et al., 1995).

The transition from animal models to a non-invasive measurement of human cortical excitability was favored by the advent of transcranial magnetic stimulation (TMS) (Kujirai et al., 1993; Rothwell et al., 2009; Ziemann et al., 1996), which has shed new light on the effects of SD on epileptic and healthy subjects. The most frequently addressed TMS parameters include motor threshold (MT), motor-evoked potential amplitude and silent period, via the single-pulse technique, and short-latency intra-cortical inhibition (SICI) and facilitation (SICF), via the paired-pulse technique. MT is considered to reflect the excitability of neuronal membranes, and its reduction is ascribed to an increase in membrane excitability of the cells presynaptic to corticospinal neurons (Ziemann et al., 1996). Conversely, SICI and SICF putatively reflect the excitability of distinct interneuronal populations, relying on γ-aminobutyric acid A ($GABA_A$)-ergic and glutamatergic transmission, respectively (Liepert et al., 1997; Ziemann et al., 1995).

Manganotti et al. (2006) used TMS to test the effects of total SD on motor cortex excitability in juvenile myoclonic epilepsy patients and healthy controls, both serving as their own baseline. SD induced a decrease in MT, a reduction in SICI and an increase in SICF in the epileptic subjects compared with baseline, whereas no significant changes were noticed in the control group. Interestingly, the SD-induced variation in motor cortical excitability, shown by the TMS parameters, was often paralleled by an increase in paroxysmal activity. The reduction in SICI and the increase in SICF were interpreted to represent a change in the cortical balance of inhibition and excitation, with a potentiation of excitation, eventually leading to a lower epileptic threshold (Manganotti et al., 2006).

Another TMS study by Badawy et al. (2006) evaluated the role of SD in patients with idiopathic generalized epilepsy (IGE), focal epilepsy, and in healthy controls. In addition to MT, SICI, SICF, they also assessed long-interval intracortical inhibition (LICI), which supposedly addresses the activity of another interneuronal, $GABA_B$-mediated circuit, presynaptic to the SICI pathway (Mott and Lewis,

1994). No intra- and inter-group changes in membrane excitability, reflected by MT values, were detected after SD. Decreased SICI, increased SICF, and decreased LICI after SD were shown bilaterally in IGE, in the hemisphere ipsilateral to the epileptic focus in focal epilepsy patients, but not in healthy controls. The authors thus concluded that SD could influence the activity of excitatory and inhibitory interneuronal networks, supposed, in turn, to modulate the excitability of corticospinal neurons. They also speculated that the enhancement of glutamatergic transmission and the reduction in GABAergic transmission might explain the SD-induced increase in cortical excitability. Interestingly, this phenomenon could also display some syndrome specificity (Badawy et al., 2006).

Another TMS study assessing the effects of partial SD on brain excitability in juvenile myoclonic epilepsy patients and healthy controls was recently conducted by Del Felice et al. (2011). After SD, the authors obtained a marked increase in cortical reactivity in epileptic subjects, as reflected by an enhanced amplitude of the late component of TMS-evoked potentials. Only a trend toward an increased cortical excitability was instead observed in healthy controls (Del Felice et al., 2011). Unfortunately, many conflicting views emerge when the studies on the influence of SD on TMS parameters in healthy controls are considered (Civardi et al., 2001; De Gennaro et al., 2007; Huber et al., 2013; Kreuzer et al., 2011; Manganotti et al., 2001; Placidi et al., 2013; Scalise et al., 2006).

In conclusion, SD appears to induce a powerful enhancement in brain excitability in several animal models as well as in humans. The elucidation of the mechanisms underlying this effect is far from definitive, and the putative involvement of distinct cortical interneuronal circuits, postulated by TMS studies, still needs to be proven. In addition, the studies described thus far lead us to the following statements: (a) a significant modification of cortical excitability after SD in human volunteers is controversial, as opposed to the constant demonstration of this effect in epilepsy patients; (b) in animal models, the effect of strong epileptogenic insults (i.e. kindling or different chemoconvulsants) is increased by SD, while the pure effect of SD in electrophysiologic parameters similar to those tested by TMS has not been assessed; (c) in humans, most data have been obtained in IGE, while only few patients with focal seizures have been studied thus far. Nonetheless, the fact that a powerful effect of SD encompasses different species that are phylogenetically distant from one another, confirms that SD and seizures/cortical excitability are strongly associated with each other.

Among the potential neuromodulators of cortical excitability, monoamines, such as serotonin and norepinephrine, are crucial candidates, especially in light of their well-established role in the vast majority of the seizure models tested so far (Giorgi et al., 2004). Only conflicting and scarce data exist about the alteration of monoaminergic transmission after SD (Rechtschaffen and Bergmann, 2002), and have been obtained only in non-epileptic rodents. Although we will not go into further detail on the literature on this aspect, the role of norepinephrine in the effects of SD on seizure susceptibility might deserve further ad-hoc investigations in the future, given its influence on vigilance/sleep–wake cycle (España and Scammell, 2011), and its ability to modulate epileptogenicity (Giorgi et al., 2004).

4. Inhomogeneity of the studies addressing SD EEG in epilepsy

As already reported above, an "activating" effect of SD on the EEG of epileptic patients is unanimously accepted, with the earliest related studies dating back more than 50 years. Yet, the results of these papers are difficult to compare, mainly for the following reasons: (1) differences among SD and EEG protocols; (2) inhomogeneity of the patients tested; (3) variability in the outcome parameters.

Table 1 shows a concise list of all the studies performed from 1960 onwards, underscoring the main discrepancies in their methodological protocols.

4.1. Methodological differences

It is particularly surprising how most studies addressing the role of SD EEG in epilepsy differ methodologically, especially with respect to: (1) duration of SD; (2) EEG protocols; (3) duration of EEG after SD; (4) occurrence of wakefulness during SD EEG; and (5) time of the day when SD EEG was acquired.

The length of SD is potentially a crucial parameter, and varies significantly in the majority of the studies. This aspect could be particularly relevant in light of evidence showing that the duration of SD in animal models is strictly related to EEG parameters, such as power density in the delta band (Dijk et al., 1990; Tobler and Borbély, 1986).

As shown in Table 1, the duration of SD varies considerably among centers, ranging from 3 to 36 h.

In most research studies on adults, SD was induced for at least 24 h before the EEG, while partial SD protocols have mainly been tested in the last 10–15 years (Table 1). No specific surveys detailing the average length of SD protocols for clinical purposes have been published in recent years. To our knowledge, many European epilepsy centers employ a 24-h SD protocol for clinical investigations. The possible rationale for this might stem from the predominance of a 24-h duration of SD in the initial studies, and from such a recommendation in the only EEG ILAE guidelines available to date (Flink et al., 2002).

Many authors prefer to apply age-related partial SD protocols for children (Table 2). Such an approach is based on the assumption that children are more prone to the activating effects of sleep and SD than adults. However, the duration of SD for each age subcategory appears to have been arbitrarily determined by the different authors, and this significantly hinders study comparison (Table 2).

A baseline EEG followed by an SD EEG was the mostly adopted in the study protocols. Only a few reports also examined an additional second baseline EEG or a second SD EEG, to allow for the exclusion of a sampling effect (see Table 1 and Section 6.1). Few other studies also performed an additional EEG during spontaneous sleep, either within a continuous EEG monitoring protocol (Halász et al., 2002a; Malow et al., 2002) or during an afternoon nap (Molaie and Cruz, 1988; Drake et al., 1990). In some reports, the authors compared a routine EEG and/or an SD EEG with a sleep EEG induced by drugs (Fig. 1). A more complex protocol was used in selected studies: DeRoos et al. (2009) randomized different subjects either to a routine wake EEG or to an SD EEG, while Roupakiotis et al. (2000) recorded a routine EEG and subsequently randomized their subjects to a second routine EEG, an SD EEG, or a drug-induced sleep EEG. Gilbert et al. (2004) did not acquire a baseline EEG for all their patients, but randomized them to a baseline EEG, an EEG following total SD, or an EEG after partial SD.

A factor which is particularly critical for both the interpretation and comparison of the different study results is the duration of baseline and SD EEGs. As a general rule in the clinical setting, routine EEG recordings should not last less than 20 min and should include hyperventilation, intermittent photic stimulation (IPS), and, occasionally, spontaneous sleep. This protocol has been used for the majority of studies specifying the duration of their baseline EEG, although a consistent number of papers do not provide details of this (Table 1). Whether sleep occurred during baseline recordings is not properly specified in most reports (Table 1).

SD EEG recordings are usually longer than routine EEGs, and include wakefulness, sleep periods, hyperventilation, and IPS in

Table 1
Studies addressing the role of SD EEG in epilepsy patients.

Study	Number/age	Study type	Neuro-imaging (type)	Sub-analysis on syndromes/ seizure types	Pts. ± controls	AEDs	EEG study protocol	IEDs	Baseline EEG/result	Baseline EEG duration	SD duration/SD EEG duration	Wakefulness in SD EEG (duration)	SD EEG registration time (h)
Mattson et al. (1965)	143 pts./11–49 y.	R	N	Grand mal/ psychomotor/ other focal/myoclonic or petit mal	Epilepsy pts. vs. healthy controls	Y/N	rEEG → SD EEG → rEEG if abnormal SD EEG	Sp, Sw, S–W	Y/normal or abnormal	NS	26–28 h/≥20′	Y (NS)	NS
Pratt et al. (1968)	114 pts./NS	P	Y (CT/PNe)	Grand mal/ psychomotor/ other focal/ other	Epilepsy pts. with normal or borderline rEEG	NS	rEEG → SD EEG → rEEG if abnormal SD EEG	Sp, Sw, S–W	Y/normal or borderline	NS	24–26 h/≥20′	Y (NS)	NS
Geller et al. (1969)	37 pts./ 4–14 y.	P	N	N	Suspected epilepsy pts. vs. healthy controls	Stopped 5 days before EEGs	rEEG → SD EEG → rEEG if abnormal SD EEG	Sp, Sw, S–W	Y/normal	≥30’	24–28 h/30′	Y (NS)	Same as rEEG
Scollo-Lavizzari et al. (1975)	294 pts./2–65 y.	R	N	N	Suspected epilepsy pts. with inconclusive rEEG	NS	rEEG → SD EEG	Sw, S–W	Y/normal or borderline	NS	24–27 h/90′	Y (NS)	Morning after SD (5:30–7 am)
Scollo-Lavizzari et al. (1977)	51 pts./14–57 y.	R	N	N	Suspected epilepsy pts. with inconclusive rEEG	NS	rEEG → SD wake EEG → SD sleep EEG	Sw, S–W	Y/normal or borderline	NS	24–26 h/80–90′	Y (25′)	Morning after SD (5:30–7 am)
Roby and Greenberg (1978)	33 pts./ 5–49 y.	R	N	N	Suspected epilepsy pts. with normal or abnormal rEEG	Y/N	rEEG → SD EEG	Sp, Sw, S–W, focal SW	Y/normal or abnormal	NS	24 h/NS	NS	Morning after SD
Schwarz and Zangemeister (1978)	185 pts./15–69 y.	R	N	Generalized/ psychomotor/ unclarified disturbances of consciousness	Suspected and known epilepsy pts.	NS	rEEG → SD EEG	Sp, Sw, S–W	Y/normal or abnormal	11′	24 h/40–50′	Y (11′)	Morning after SD
Degen (1980)	102 pts./1–70 y.	R	N	GTCS on awakening/GTCS during sleep/absences/ random generalized/ psychomotor	Epilepsy pts. with normal or inconclusive rEEG	Y	rEEG → SD EEG	Sp, Sw, S–W	Y/normal or borderline	NS	Adults: 24–26 h, children: partial SD/64′	Y (17′)	NS
Tartara et al. (1980)	452 pts./3–68 y.	R	N	N	Pts. affected by epilepsy and other neurological diseases	NS	rEEG → SD EEG	Sp, Sw, S–W,SW	Y/normal or abnormal	NS	24–36 h/84′	Y (24′)	NS
Degen and Degen (1981)	115 pts./ 1–>40 y.	P	N	CPS/SGTCS	Epilepsy pts. with CPSs	Y	rEEG → DI sleep EEG → SD EEG	Sp, Sw, S–W	Y/normal or abnormal	NS	24–26 h/44′	Y (17′)	NS
Rowan et al. (1982)	43 pts./ 5–51 y.	R	N	N	Suspected epilepsy pts. with normal or inconclusive rEEG	NS	rEEG → DI sleep EEG → SD EEG	NS	Y/normal or abnormal	NS	Adults: 24–26 h, children: partial SD/≥30′	Y (NS)	NS
Degen and Degen (1983)	32 pts./15–51 y.	R	N	Atypical absences (±other seizure types)	Epilepsy pts. with atypical absences and normal rEEG	Y	rEEG → DI EEG → SD EEG	Sp, Sw, S–W	Y/normal	NS	24–26 h/NS	NS	NS
Veldhuizen et al. (1983)	72 pts./30.3 ± 11.5 y.	P	N	Primary generalized/ secondary generalized/ partial epilepsy	Suspected epilepsy pts. with normal or inconclusive rEEG	Y/N	rEEG → DI EEG → SD EEG (random order)	Sp, Sw, S–W	Y/normal or abnormal	30′	24–26 h/40′	Y (10′)	Morning after SD (8:30 am)

Table 1 (*Continued*)

Study	Number/age	Study type	Neuro-imaging (type)	Sub-analysis on syndromes/ seizure types	Pts. ± controls	AEDs	EEG study protocol	IEDs	Baseline EEG/result	Baseline EEG duration	SD duration/SD EEG duration	Wakefulness in SD EEG (duration)	SD EEG registration time (h)
Deisenhammer et al. (1984)	236 pts./ 39.7 y.	R	N	N	Patient with a history of alcoholism ± seizures	NS	rEEG → SD EEG	Sp, mSp, Sw, S–W, SW	Y/normal or abnormal	NS	24 h/30–60′	Y (NS)	Morning after SD
Logothetis et al. (1986)	85 pts./40–67 y.	P	Y (CT)	N	Pts. with "typical" vs. "atypical" seizures	NS	wake rEEG → wake SD EEG	Sp, Sw, S–W	Y/normal	20'	24 h/20′	Y (20′—not including sleep)	NS
Roth et al. (1986)	434 pts./NS	R	Y (CT)	Grand mal/ petit mal/ psychomotor-focal–visceral epilepsy/ combined forms	Pts. with suspected epilepsy or other neurological diseases	NS	rEEG → SD EEG	Sp, Sw, S–W	Y/normal or abnormal	NS	Age-related SD/90′	Y (NS)	Morning after SD
Degen et al. (1987)	190 pts./NS	R	N	GTCS on awakening-during sleep-other/ SPS/CPS/ myoclonic-astatic	Epilepsy pts. with normal rEEG	Y	rEEG → DI EEG → SD EEG	NS	Y/normal	20'	24 h/60′	Y (20′)	NS
Molaie and Cruz (1988)	8 pts./ 29–63 y.	P	Y (CT)	CPS	Pts. with CPS and abnormal rEEG	Y	cEEG → SD cEEG	Sp, S–W	Y/abnormal	7 h (cEEG)	36 h/7 h	Y (NS)	Night after SD
Clemens (1989)	51 pts./NS	P	N	N	Epilepsy pts. seizure-free for at least 3 years	Y (NS)	SD EEG (no rEEG)	NS	N	N	24 h/60′	Y (NS)	Morning after SD
Drake et al. (1990)	100 pts./16–61 y.	R	Y (CT/MRI)	CPS/GTCS/ mixed seizures	Epilepsy pts. with refractory atypical seizures	NS	post-prandial nap EEG → SD EEG	NS	N	N	24 h/8–10 h	Y (8–10 h–not including sleep)	Morning after SD
Degen and Degen (1991)	240 pts./NS	R (in review)	N	GTCS on awakening/ GTCS during sleep/ CPS/absence	Epilepsy pts. with normal rEEG	Y (NS)	rEEG → DI EEG or SD EEG	NS	Y/normal and abnormal	NS	24 h/NS	NS	NS
Gastaut et al. (1991)	250 pts./NS	R	N	N	Suspected epilepsy pts.	Stopped 24 h before EEG	SD + DI nap EEG (no rEEG)	NS	N	N	4 h/40–60′	N	Early afternoon nap (12:30–2 pm)
Kubicki et al. (1991)	655 pts./ <1 to >70 y.	R	N	N	Pts. with suspected epilepsy or other neurological diseases	NS	rEEG → SD EEG	Sp, mSp, Sw, S–W	Y/normal and abnormal	NS	Age-related SD/75–105′	Y (45′)	Early afternoon nap (12:30–2 pm)
Borkowski et al. (1992)	21 pts./ 5–12 y.	P	N	Suspected absence seizures only	Suspect absences + LD vs. history incompatible with absences + LD vs. healthy controls	N	DI rEEG → SD EEG	S–W < 4 Hz	Y/normal	NS	24 h/NS	NS	Morning after SD
Thomaides et al. (1992)	236 pts./43.5 ± 12.5 y.	P	Y (CT)	N	Epilepsy pts. ± history of head injury vs. healthy controls	Y	rEEG → SD EEG	Sp, Sw, S–W	Y/normal or borderline	20′	24 h/20′	Y (20′–not including sleep)	Morning after SD
Aguglia et al. (1994)	41 pts./17–67 y.	P	N	Adult-onset partial epilepsy syndromes	Partial epilepsy pts. not in AEDs vs. partial epilepsy pts. in AEDs vs. controls	Y (50%) N (50%)	rEEG → DI sEEG → SD EEG	Sp, Sw, S–W	Y/normal	NS	24 h/4–5 h	Y (NS)	Morning (9:30 am)

El-Ad et al. (1994)	76 pts./17–85 y.	R	N	N	Suspected or established epilepsy pts.	Y/N	SD + DI wake and sleep EEG	Sp, Sw	N	N	24–26 h/45′	Y (15′)	NS
So et al. (1994)	101 pts./15–84 y.	R	N	CPS/Generalized seizures	Temporal lobe epilepsy pts. with a normal rEEG	Y/N	rEEG → SD EEG	Sp, Sw, S–W	Y/normal	NS	NS/90′	NS	NS
Carpay et al. (1997)	560 pts./ 1 m.–16y.	P	N	SPS/CPS/GTCS/ myoclonic/ atonic/absences	Suspected epilepsy pts.	Y/N	rEEG → SD EEG (if normal rEEG)	Sp, Sw, S–W, SW	Y/normal or abnormal	NS	Age-related SD/90′	Y (NS)	Early afternoon
Fountain et al. (1998)	29 pts./ 3–68 y.	R	N	N	Epilepsy pts. with normal rEEG	Y/N	rEEG → SD EEG	Sp, Sw, S–W	Y/normal	30’	24 h/39′	Y (NS)	Morning after SD
King et al. (1998)	300 pts./5–83 y.	P	Y (MRI/CT)	N	Suspected epilepsy pts.	N	rEEG → SD EEG (if normal rEEG)	Sp, Sw, S–W,SW	Y/normal or abnormal	30’	Age-related SD/40′	Y (NS)	Morning after SD
Liporace et al. (1998)	46 pts./NS	P	N	Focal/ Generalized seizures	Suspected epilepsy pts. and normal or borderline rEEG	NS	rEEG → SD EEG → ambulatory EEG	Sp, Sw, S–W, mS–W	Y/normal or unspecific	NS	3–4 h/30–60′	Y (NS)	NS
Liamsuwan et al. (2000)	493 pts./ 1 m.–>5 y.	R	N	N	Pts. affected by known or suspected epilepsy	NS	partial SD EEG	Sp, Sw, S–W, SW	N	N	Age related SD/90′	Y (NS)	NS
Roupakiotis et al. (2000)	721 pts./17–75 y.	R	N	N	Suspected epilepsy pts. vs. pts. with other neurological disorders	NS	rEEG → SD EEG or DI sEEG or 2nd rEEG	Sp, Sw, S–W	Y/normal or abnormal	45’	24 h/60′	Y (NS)	NS
Marinig et al. (2000)	19 pts./14–71 y.	R	N	Focal/ generalized epilepsies	Epilepsy pts. with normal or inconclusive rEEG	Y	rEEG → sleep EEG (some) → SD EEG (all)	Sp, Sw, S–W	Y/normal or borderline	NS	NS/NS	NS	Early afternoon
Peraita-Adrados et al. (2001)	686 pts./NS	R	N	N	Suspected epilepsy pts. with a normal rEEG	N	rEEG → partial SD EEG → 2nd partial SD EEG for some	Sp or Sw, SW, mSW	Y/normal	20’	Age-related SD/120–150′	Y (30′ for some/NS for other pts.)	Early afternoon (1–3/3.30 pm)
DellaBadia et al. (2002)	69 pts./11–66 y.	R	Y (MRI-PET)	N	Focal epilepsy pts. in pre-surgical evaluation	Y	rEEG → SD EEG	Sp, Sw, SW	Y/normal or abnormal	NS	2 h/NS	NS	NS
Halász et al. (2002a)	10 pts./20–46 y.	P	Y (CT + MRI)	JAE/JME/GTCS on awakening	IGE pts.	Y	cEEG 24 h × 4 (wake, sleep, and post-SD)	S–W	Y/abnormal	cEEG	24 h/24 h	Y (NS)	cEEG
Malow et al. (2002)	84 pts./ 38 ± 9.7 y.	P	MRI	CPS/SGTCS	Refractory partial epilepsy pts.	Y (tapering)	SD EEG monitoring vs. EEG monitoring	seizure	Y/abnormal	cEEG	24 h/NS	Y (NS)	cEEG
Gilbert et al. (2004)	820 pts./0–18 y.	R	N	N	Suspected epilepsy pts.	Y	rEEG vs. SD EEG vs. partial SD EEG	NS	Y/normal or abnormal	20’-30’	Age-related SD-partial SD/20–30′	Y (NS)	Morning after SD
Sousa et al. (2005)	41 pts./ 16–50 y.	R	N	JME pts. only	Suspected JME pts.	Y/N	rEEG → SD EEG	Sp, Sw, S–W, mS–W, SW	Y/normal or abnormal	25–35′	NS (24 h′)/>50′	Y (NS)	Morning after SD (7 am)
Leach et al. (2006)	98 pts./ 15.7–22.1 y.	P	N	N	Suspected epilepsy pts.	N	rEEG → SD EEG → DI sEEG (in random order)	S–W,SW	Y/normal or abnormal	22′	24 h/40′	Y (NS)	NS
DeRoos et al. (2009)	206 pts./ 5 m.–18y.	P	N	N	Suspected epilepsy pts.	Y/N	rEEG vs partial SD EEG	Sp, Sw, S-W, mS–W, SW	NS	30’	age-related SD/30′	Y (NS)	Morning after SD (8 am)
Shahar et al. (2010)	55 pts./ 5–18 y.	R	N	Focal/ Generalized seizures	Pts. ≥2 recurrent seizures and normal rEEG	N	rEEG → SD EEG	Sp, SW	Y/normal	30’	6 h/≥30′	Y (NS)	Morning after SD

Table 1 (*Continued*)

Study	Number/age	Study type	Neuro-imaging (type)	Sub-analysis on syndromes/ seizure types	Pts. ± controls	AEDs	EEG study protocol	IEDs	Baseline EEG/result	Baseline EEG duration	SD duration/SD EEG duration	Wakefulness in SD EEG (duration)	SD EEG registration time (h)
Gandelman-Marton and Theitler (2011)	78 pts./18–78 y.	R	Y (CT)	Focal/SGTCS	Suspected epilepsy pts.	N	rEEG → SD EEG	Sp, Sw, S–W, mS–W, S–W	Y/normal	20′-30′	2–3 h/38–70′	Y (NS)	NS
Giorgi et al. (2013)	131 pts./ 41 ± 12 y.	R	Y (MRI)	Focal symptomatic/ focal probably symptomatic/ generalized epilepsies	Suspected epilepsy pts. with normal rEEG vs. non-epilepsy pts.	N	rEEG → SD EEG → rEEG if abnormal SD EEG	Sp, Sw, S–W	Y/normal or abnormal	NS	26–28 h/≥20′	Y (NS)	NS

Abbreviations: AED(s) = anti-epileptic drug(s); cEEG: continuous EEG monitoring; CPS(s) = complex partial seizure(s); CT = computed tomography; EEG = electroencephalogram; h = hour; IED(s) = interictal epileptiform discharge(s); IGE = idiopathic generalized epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; LD = learning disabilities; m. = month(s); mSp = multi-spike; mSW = multi spike-and-wave; MRI = magnetic resonance imaging; N = no; NS = not specified; P = prospective; PET = positron emission tomography; PNe: pneumoencephalography; pts.=patients; R = retrospective; rEEG = routine EEG; S–W = spike-and-wave; SD = sleep deprived/sleep deprivation; (S)GTCS(s) = (secondarily) generalized tonic-clonic seizure(s); Sp = spike; SPS(s) = simple partial seizure(s); SW = slow wave; Sw = sharp wave; Y = yes; y. = year(s).

most cases. Their duration generally spans from 30 to 90 min, with a discrete variability across studies. Some protocols included an SD EEG lasting longer than 90 min, while a few studies conducted a continuous EEG lasting up to 24 h after SD (Table 1). Considerable inhomogeneity is observed with respect to the distribution of wakefulness and sleep periods in the SD EEG: while the presence of sleep appears to be the rule in the SD EEGs, with only few exceptions, the same cannot be stated for wakefulness (Table 1). The time of day when SD EEG is acquired could also represent a potentially relevant variable. The interplay between the circadian and the homeostatic factors occurring during daytime sleep differs from that occurring during nocturnal sleep. However, this information was lacking in the majority of reports.

4.2. Populations analyzed

The features of the patients analyzed in the studies evaluating SD EEG appear to be very variable, too. This is not a matter of inhomogeneous methodology, but is related to the different experimental or clinical questions addressed in each study. While most authors included patients with pre-existing basal EEGs, in some reports, the first routine EEG was acquired during the study. Many papers examined patients with epilepsy or suspected epilepsy with normal or borderline routine EEGs. In others, the existence of a previous EEG showing epileptiform abnormalities was not exclusion criterion (Tables 1 and 2).

Most studies included patients with different seizure/epilepsy types, often only vaguely classifying them (Table 1). Remarkably, there is a lack of information about seizure/syndrome types in both older and more recent studies (Table 1). In addition, details of neuroimaging [computed tomography (CT)/MRI] were sporadically added to the semiology data. Giorgi et al. (2013) conducted the only study to date in which the clinical characteristics of a large patient population were thoroughly classified into syndromes and subsyndromes, with the effects of SD being evaluated accordingly.

Several studies included children in addition to adults, while others only studied pediatric populations (Tables 1 and 2).

Ongoing AED therapy is a bias which potentially and unpredictably affects EEG results (Duncan, 1987; Marciani et al., 1996; Placidi et al., 2004). Unfortunately, drug-naïve patients were only included in a few studies, and detailed descriptions of medications for patients on AEDs were often not given (Table 1). Another factor potentially hindering comparison of these studies is the discontinuation or tapering of AEDs included in some protocols (Gastaut et al., 1991; Geller et al., 1969; Malow et al., 2002).

4.3. Outcome parameters

In most SD EEG studies, only patients with normal or unspecific routine EEGs were selected. Baseline EEG activation was generally defined as the occurrence of specific IEDs. In some reports, slow waves were included, and in many studies, the type of EEG abnormalities was not even specified (Table 1). Sample size is critical to determine the sensitivity and specificity of SD EEG. This has been systematically addressed in only three papers (DeRoos et al., 2009; Gilbert et al., 2004; Malow et al., 2002), which defined sample sizes after power calculations based on pre-set outcome measures. The number of patients studied generally ranged between 50 and 80, although the actual sample sizes in the individual studies ranged from 8 to 820 (Table 1).

Most studies addressing the role of SD EEG in epilepsy are retrospective, although several prospective papers have also been published (Table 1).

In conclusion, the extreme variability in population features and methodology significantly hinders study comparisons. Many important papers were published before the first widely accepted

Table 2
EEG after sleep deprivation: study protocols and results in pediatric patients.

Reference	Patient number	Age	Patients ± controls	EEG study protocol	SD duration	SD EEG activation rate
Geller et al. (1969)	37	4–14 y.	Suspected epilepsy patients vs. controls	rEEG → SD EEG → rEEG if abnormal SD EEG	24–28 h	32% in patients (8% in healthy controls)
Degen (1980)	48	1–20 y.	Epilepsy patients with normal or inconclusive rEEG	rEEG → SD EEG	Children: partial SD (4–6 h sleep)	≈66%
Tartara et al. (1980)	131	3–18 y.	Patients affected by epilepsy and other neurological diseases	rEEG → SD EEG	24–36 h	54% in patients (18% in controls with other neurological diseases)
Kubicki et al. (1991)	275	5–14 y.	Patients with suspected epilepsy or other neurological diseases	rEEG → SD EEG	Age-related partial SD: age < 4 y: 2 h age 4–14 y: 3 h age > 14 y: 4 h	48%
Borkowski et al. (1992)	21	5–12 y.	Suspect absences + LD vs. history incompatible with absences + LD vs. healthy controls	DI EEG → SD EEG	24 h	89% in patients (17% in controls with history incompatible with absences + LD)
Carpay et al. (1997)	560	1 m.–16y.	Suspected epilepsy patients	rEEG → SD EEG (if normal rEEG)	Age-related partial SD: age < 2 y: no SD, EEG recorded during afternoon nap age 2–10 y: 2 h age 10–15 y: 4 h	30% (children with normal rEEG) - 44% (children with non-epileptiform abnormalities in rEEG)
Peraita-Adrados et al. (2001)	128	<15 y.	Suspected epilepsy patients with a normal rEEG	rEEG → partial SD EEG → 2nd partial SD EEG for some	Age-related partial SD: age < 1 y: 0 h age < 1–10 y: 1 h age 10–14 y: 2 h age 15–18 y: 3 h	28.1%
Gilbert et al. (2004)	820	0–18 y.	Suspected epilepsy patients	rEEG vs. SD EEG vs. partial SD EEG	Partial SD (awake 2 h after usual bedtime) or age-related SD: age < 3 y: 3 h age 3–11 y: 5 h age > 11 y: 7 h	21% partial SD EEG vs. 23% SD EEG vs. 23% rEEG
DeRoos et al. (2009)	206	5 m.–18 y.	Suspected epilepsy patients	rEEG vs. partial SD EEG	Age-related partial SD: age < 3 y: 3 h age 3–11 y: 5 h age < 11 y: 7 h	44.4% (vs. 32.3% rEEG)
Shahar et al. (2010)	55	5–18 y.	Patients ≥ 2 recurrent seizures and normal rEEG	rEEG → → SD EEG	6 h	20% (generalized seizures)–40% (focal seizures)

Abbreviations: EEG = electroencephalogram; h = hour; m. = month; rEEG = routine EEG; SD = sleep deprived/sleep deprivation; SD EEG = EEG after sleep deprivation; y. = year.

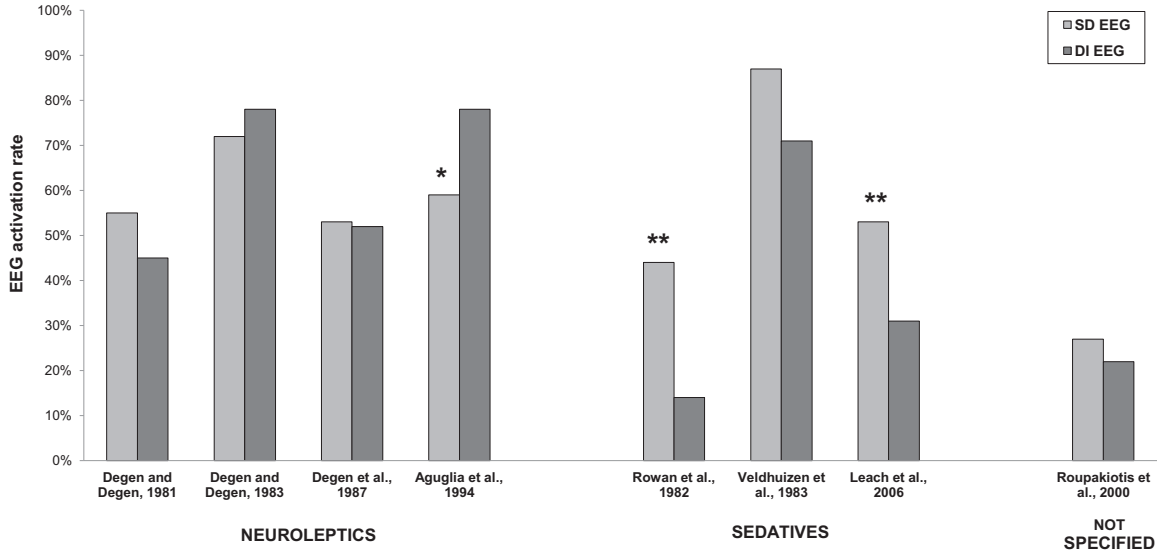

Fig. 1. Studies comparing the effects of electroencephalogram (EEG) after sleep deprivation and drug-induced sleep EEG.
The studies comparing the effects of EEG after sleep deprivation (SD EEG) and drug-induced sleep EEG (DI EEG) used dissimilar protocols and often revealed conflicting results. Their findings have been adapted here to allow for comparisons. In general, the yield of SD EEG was greater than DI EEG when sedative drugs, such as barbiturates (Rowan et al., 1982; Veldhuizen et al., 1983) or benzodiazepines (Leach et al., 2006), were used to induce sleep in DI EEG. Conversely, a higher activation rate for DI EEG was described in some studies using neuroleptic drugs, namely promazine (Degen and Degen, 1983, 1981; Degen et al., 1987) or chlorpromazine (Aguglia et al., 1994). Considering only the studies where a statistically significant threshold was achieved, SD EEG was superior to DI EEG in patients with suspected epilepsy and normal or inconclusive basal EEG (Rowan et al., 1982), and in patients with suspected epilepsy and generalized or focal interictal epileptiform discharges (Leach et al., 2006). Conversely, Aguglia et al. (1994) described a higher activation rate of DI EEGs in patients with adult-onset partial epilepsy; the difference between the two protocols was statistically significant for untreated patients, but not for treated patients. Pearson's chi-squared and/or Fisher's exact test were applied for the statistical analyses. ** $p < 0.005$; * $p < 0.05$ vs DI EEG.

ILAE seizure/syndrome classification (Commission on Classification and Terminology of the International League against Epilepsy, 1981, 1989), which further complicates the topic. We also believe that the lack of prospective, ad-hoc designed studies is another crucial aspect needing future attention.

5. Findings of the different studies

5.1. Sensitivity and specificity of SD EEG

Analysis of the available studies revealed significantly variable results with respect to the sensitivity of SD EEG. In patients with epilepsy and a normal or inconclusive routine EEG, sensitivity values ranged from 20% (So et al., 1994) to 57% (Scollo-Lavizzari et al., 1977). In a well-characterized population of epileptic adults with a normal first EEG, we have recently shown an overall IED incidence of 42.1% after SD: 39.6% in focal symptomatic epilepsies; 37.5% in probably symptomatic epilepsies; and 57.2% in generalized epilepsy patients. No statistically significant differences were seen between focal and generalized epilepsy, even when focal epilepsy subgroups were taken into consideration (Giorgi et al., 2013). As a general rule, EEG activation is more frequent when a first routine EEG shows non-epileptiform abnormalities compared with a completely normal routine EEG (Carpay et al., 1997).

Studies testing the effects of activating procedures during SD EEG seem to further increase the occurrence of IEDs versus basal SD EEG, as shown for hyperventilation (Rowan et al., 1982; Schwarz and Zangemeister, 1978; Tartara et al., 1980; Veldhuizen et al., 1983) and IPS (Geller et al., 1969; Kubicki et al., 1991; Rowan et al., 1982; Schwarz and Zangemeister, 1978; Tartara et al., 1980; Veldhuizen et al., 1983).

Most papers indicate that the specificity of SD EEG is significantly higher than the sensitivity. In age-matched healthy controls, SD EEG achieved a specificity of 92–100% (Aguglia et al., 1994; Geller et al., 1969; Tartara et al., 1980; Thomaides et al., 1992), whereas 82–100% specificity was obtained for patients with neurological disorders other than epilepsy (Deisenhammer et al., 1984; Mattson et al., 1965; Roupakiotis et al., 2000; Tartara et al., 1980). These data are particularly meaningful, since they confirm the critical role of SD EEG as a diagnostic test for patients with epilepsy.

Sensitivity and specificity data could potentially be biased as, in some cases, the diagnosis of epilepsy was confirmed or ruled out only after an SD EEG. In other words, the lack of IEDs in the SD EEG was used in several studies to confirm a non-epilepsy diagnosis. This caveat can be potentially ruled out by studies in which an SD EEG is performed on consecutive subjects after a first suspected epileptic seizure, and the SD EEG is analyzed blindly and at the beginning of the follow-up. Using this approach, the results of the SD EEG would not be influenced by the final diagnosis, formulated after a prolonged follow-up. A similar method, although in a retrospectively analyzed patient series, has been recently used and has shown high specificity of a partial SD EEG (91.1%; Giorgi et al., 2013). Prospectively reassessing the role of activating procedures during SD EEG would also be of interest, in light of the above-mentioned evidence in favor of their significant activating effect. If confirmed, these results might lead to the routine use of IPS and hyperventilation being included in the SD EEG guidelines.

5.2. Effects of SD-induced sleep versus drug-induced sleep

Studies comparing the effects of sleep EEG obtained after SD with those obtained by drug-induced sleep often reveal inconsistent results, as shown in detail in Fig. 1.

These studies are also hardly comparable as the patient populations were heterogeneous (e.g. patients with complex partial seizures, or with atypical absences, or with absence seizures), and because the drugs used to induce sleep differ significantly with regard to pharmacokinetic and pharmacodynamic properties (e.g. chlorpromazine, a neuroleptic, compared with barbiturates, which bind to $GABA_A$ receptors). Apparently, it seems that sleep induced by sedative drugs, acting on $GABA_A$ receptors, is less powerful than SD in evoking IEDs, while neuroleptics tend to induce a steeper increase in IED yield during sleep than SD EEG (Fig. 1). This is not unexpected, in light of the clinical data showing a similar trend for the influence of these classes of drugs on seizure threshold as well (Lee et al., 2003).

Nowadays, neuroleptic-induced sleep EEG is no longer proposed for patients with epilepsy, due to ethical reasons and to the similar efficacy of SD in evoking IEDs (Fig. 1).

5.3. Effects of SD-induced sleep versus naturally occurring sleep

Several authors claim that the activating potential of sleep following SD is greater than that of sleep per se. Although this is a crucial issue, direct comparison of the two protocols has only been conducted in a few studies. Some of them provided convincing evidence in favor of an additional activating effect of SD compared with baseline sleep. In a homogeneous population of patients affected by complex partial seizures and frequent focal IEDs, Molaie and Cruz (1988) compared baseline whole-night sleep and nocturnal sleep after 36 h of SD, observing a consistent post-SD increase in IEDs during NREM sleep stage 2. In their elegant study, Fountain et al. (1998) examined a post-SD EEG in patients with a baseline sleep EEG lacking IEDs, and observed EEG activation in 52% of the patients, with IEDs prominently occurring during sleep. In a continuous EEG monitoring study on patients with IGE, Halász et al. (2002a) also showed a consistent increase in IED duration and density in post-SD sleep EEG compared with pre-SD levels.

More ambiguously, Drake et al. (1990) noted the enhancement of generalized discharges during spontaneous sleep, and an increase in focal discharges during post-SD sleep. Conversely, Gilbert et al. (2004) conducted one of the few studies denying an independent role of SD, neither partial nor age-related whole-night SD, in increasing IED prevalence during subsequent sleep in a pediatric population. Marinig et al. (2000) reported preliminary evidence of no differences between sleep EEG without SD and sleep EEG post-SD, but the lack of a detailed explanation of the protocols employed does not allow for a proper evaluation of their results.

In summary, SD-induced sleep seems to be more likely to evoke IEDs than natural sleep, at least in adult patients. Sleep instability and the microstructural features potentially explaining these findings are discussed in Section 6.3.

5.4. Role of SD EEG in different epilepsy syndrome/seizure types and correlations with neuroimaging data

Only a few studies attempted to detect a correlation between SD activation and *seizure types*, and, surprisingly, most of them even date back to the pre-ILAE seizure-classification era (Fig. 2) (Commission on Classification and Terminology of the International League against Epilepsy, 1981). This might be the reason why different and even opposite results can be found in studies comparing generalized and focal seizures.

With respect to the correlation between SD EEG effects and the different epilepsy *syndromes*, a prevalence of studies showing a stronger effect of SD on IGE versus focal epilepsy can be found. Concerning focal seizures, the only study assessing potential discrepancies between focal symptomatic epilepsy and probably symptomatic epilepsy did not reveal any significant differences in EEG activation (39.6% vs. 37.5%, respectively; Giorgi et al., 2013).

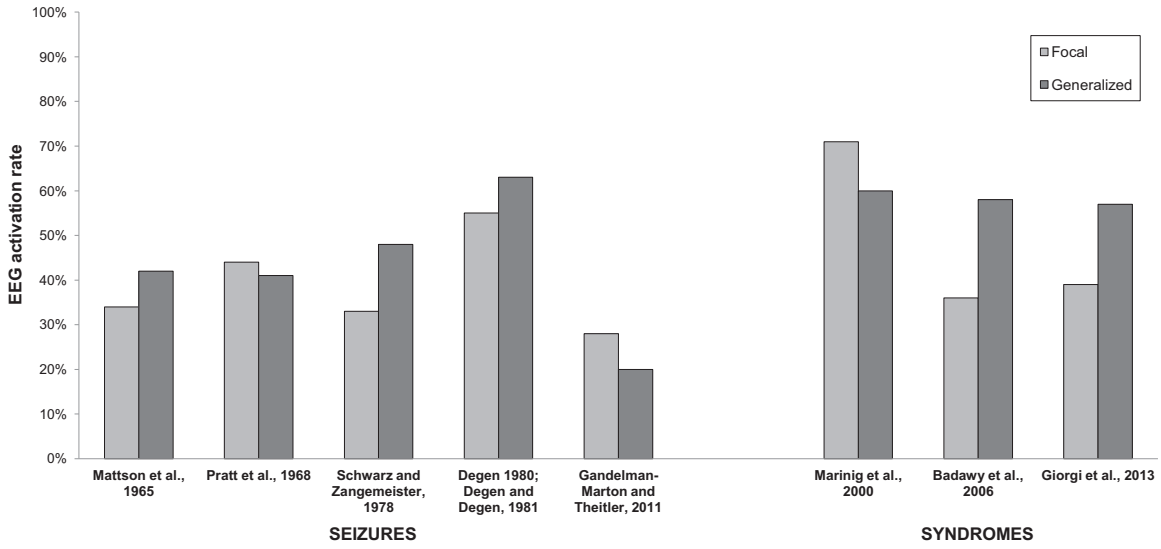

Fig. 2. *Activation of the electroencephalogram (EEG) after sleep deprivation according to different seizure/syndrome types.* The figure shows the available data for the activation rates of EEG after sleep deprivation (SD EEG) according to different seizure or syndrome types. The individual results regarding both syndrome and seizure types have been adapted to create two categories, "generalized" and "focal", to allow for comparisons across studies. When taken into account, secondarily generalized seizures have been included in the "focal" category. Several studies were conducted before the first ILAE seizure and syndrome classifications, and often categorized seizures differently. Although the majority of the studies showed a stronger effect of SD EEG for patients presenting with generalized seizures or diagnosed with generalized epilepsy syndromes, statistical significance was not achieved in any paper. Pearson's chi-squared and/or Fisher's exact test were applied for the statistical analyses.

One of the main targets of SD EEG is represented by patients potentially affected by "probably symptomatic" epilepsy (previously referred to as "cryptogenic focal epilepsy") in which neuroimaging is unremarkable or unspecific. Neuroimaging data are only available in a few papers, in which details are often insufficient: symptomatic lesions are generically reported as "brain lesions" (Roth et al., 1986), "post-traumatic epilepsy" (Thomaides et al., 1992), or even just as "abnormal CT scans" (Gandelman-Marton and Theitler, 2011) (Table 1). Attempts to detect correlations between neuroimaging findings and SD EEG results have been scarcely carried out; when available, they are mostly generic and inconclusive. In a recent study with a more detailed analysis of neuroimaging data, the presence of IEDs in SD EEGs of patients with focal symptomatic epilepsy did not correlate with the cause of epilepsy when comparing the three main etiology groups, i.e. vascular, malformative, and hippocampal sclerosis (Giorgi et al., 2013).

5.5. The influence of clinical variables on SD EEG effects

Some studies showed that the likelihood of activation is influenced by specific clinical features, including severity of epilepsy, disease familiarity, and concomitant neurologic disorders, although the differences were not always statistically significant (Table 3).

The question about the influence of AEDs is also controversial. Although the majority of the patients enrolled in the above-mentioned studies were already taking AEDs (Table 1), in some studies, AEDs did not appear to influence the likelihood of activation after SD (Fountain et al., 1998; Gilbert et al., 2004; Mattson et al., 1965). Opposite findings have also been reported (Pratt et al., 1968). Several groups recently addressed the effects of AEDs on epileptiform discharges, sleep structure, and daytime sleepiness, and gave different results depending on the drug assessed (Bonanni et al., 2001, 2004; Jain and Glauser, 2014; Placidi et al., 2000; Sammaritano and Sherwin, 2000). Thus, an effect of AED therapy on the sensitivity and specificity of SD EEG should also be taken into account.

A powerful EEG activation after SD was consistently reproduced in children with epilepsy, especially those older than 3 years (DeRoos et al., 2009). Because of this proneness, many authors have used partial SD graded for age in children over the last decades (Tables 1 and 2). The existence of an age-related grading in SD duration, often varying significantly among studies, impedes comparison of the sensitivity values of SD EEG between children and adults, and does not help to further clarify the role of SD in the pediatric setting. Similar to studies on adults, pediatric patients were often not categorized according to etiology (Table 1), which additionally complicates further interpretations and specific conclusions.

5.6. SD EEG and epilepsy prognosis

One of the main ambitions in epileptology is the possibility to foresee the recurrence of seizures after medication withdrawal. Surprisingly, the issue of the prognostic role of SD EEG has been tested only by Clemens (1989), who discontinued AEDs in 40 children, seizure-free for more than 3 years and with a normal SD EEG, and observed a seizure relapse in only two of them. This author proposed that the absence of IEDs in SD EEG could represent a good indicator of remission in children.

Only a single study focused on the utility of SD EEG in predicting the feasibility of epilepsy surgery (DellaBadia et al., 2002). These authors showed that the combination SD EEG and MRI were the least expensive and the best predictors to select candidates for surgical treatment.

6. Explanations for the effects of SD EEG on the occurrence of IEDs

6.1. Sampling or specific effect of SD EEG?

The EEG activation seen after SD might not only represent the effect of SD, but could also be due to a sampling effect; in other words, the mere repetition of another EEG by itself, independently of the SD effect, could increase EEG sensitivity. This issue is particularly relevant to correctly estimate the specificity and sensitivity of SD EEG and its convenience for the diagnosis of epilepsy, and it has been addressed in several studies. With this purpose, some authors

Table 3
Clinical features associated with higher likelihood of EEG activation after sleep deprivation.

Factors	Reference
Recent seizures occurrence	Degen (1980), Degen and Degen (1983), Gandelman-Marton and Theitler (2011), Pratt et al. (1968)
Earlier or recent seizure onset	Degen (1980), Degen and Degen (1991, 1983), Degen et al. (1987)
Previous history of repeated seizures	DeRoos et al. (2009), Gandelman-Marton and Theitler (2011)
Higher seizure frequency	Degen and Degen (1983)
Delayed psychomotor development	Degen (1980), Degen and Degen (1983), Degen et al. (1987)
Coexistent neuropathological conditions	Degen (1980), Degen and Degen (1983), Degen et al. (1987)
Personality changes	Degen and Degen (1983)
Family history of epilepsy	Degen et al. (1987)
Female gender	Degen and Degen (1991, 1981), Degen et al. (1987)
Children and young patients	Degen (1980), Degen and Degen (1991), Degen et al. (1987), Roth et al. (1986), DeRoos et al. (2009)

in the 1960s performed an additional basal EEG in those patients in whom SD EEG had shown IEDs. The proportion of SD-positive patients showing IEDs in a second basal EEG ranged from 18.8% (Mattson et al., 1965) to 12.8% (Pratt et al., 1968) and to a striking 0% in Geller et al. (1969). Several decades later, Roupakiotis et al. (2000) reported a positive SD EEG in 22.5% of epilepsy patients, while a second routine EEG in a separate patient group yielded IEDs in 9.6% of the cases. However, the striking difference in patient number between the two groups (178 vs. 52, respectively) slightly attenuates the relevance of these findings. A specific SD effect was also suggested in the only prospective study to date (Leach et al., 2006), which addressed the role of a sampling effect. The authors submitted 85 patients with suspected epilepsy to routine EEG, SD EEG, and drug-induced EEG in a random order, and reported that SD EEG was significantly more likely to show epileptiform discharges than the routine and drug-induced EEGs. More recently, when addressing this issue in a relatively large population of patients with a normal first basal EEG, we further confirmed that the potential of SD EEG to induce IEDs was significantly higher than that of a second routine EEG. This proved to be valid not only for patients with symptomatic focal epilepsy or probably symptomatic epilepsy ($p = 0.001$), but also for focal epilepsies analyzed as a whole (Giorgi et al., 2013).

In conclusion, there is convincing evidence that the specificity of SD EEG is independent of any sampling effect in epilepsy patients with a normal basal EEG. Leach et al. (2006) even calculated that the use of SD EEG as the first protocol in young subjects with suspected epilepsy could reduce the number of EEG requests by approximately 45%.

6.2. Specific effect of SD or simple effect of drowsiness/sleep?

Another critical issue in the interpretation of SD EEG results is whether EEG activation after SD is due to increased drowsiness, to a specific effect of SD itself, or to both of these aspects. Many studies suggest a specific activating effect of SD *per se*, pointing out that EEG activation is already present during the waking phases of the EEG recorded after SD (Degen, 1980; Degen and Degen, 1983; Degen et al., 1987; DeRoos et al., 2009; Mattson et al., 1965; Pratt et al., 1968; Schwarz and Zangemeister, 1978; So et al., 1994; Tartara et al., 1980). Fountain et al. (1998) specifically addressed this aspect and showed significant IED incidence both during wakefulness and sleep SD EEG epochs, inferring that the EEG activation was exclusively due to SD, rather than to the occurrence of sleep. Conversely, other authors suggested that EEG activation after SD might be related to the time spent in sleep or in drowsiness (Peraita-Adrados et al., 2001; Veldhuizen et al., 1983), or to a combination of the provocative effects of both SD and sleep/drowsiness (Geller et al., 1969; Scollo-Lavizzari et al., 1977). Roupakiotis et al. (2000) reported that no specific conclusions about the contribution of sleep to the efficacy of SD could be drawn, after finding a similar activation rate in SD EEGs with and without sleep epochs.

However, it must be emphasized that epileptiform discharges in SD EEGs frequently occur during the sleep phase. This has been repeatedly observed during the light sleep stages (Degen, 1980; Degen et al., 1987; Degen and Degen, 1981, 1991; Gandelman-Marton and Theitler, 2011; Molaie and Cruz, 1988; Peraita-Adrados et al., 2001; Veldhuizen et al., 1983), and also during deep sleep (Halász et al., 2002a; Roth et al., 1986).

On balance, most authors, including ourselves, lean toward the viewpoint of a specific effect of SD, independent of the SD-induced drowsiness or sleep. We recognize that this issue needs to be clarified in future ad-hoc investigations.

A potential mechanism through which SD may exert its specific activating effects on seizures, independently of the sleep rebound, is by increasing cortical excitability after prolonged wakefulness, as shown by TMS studies performed in patients with either generalized or focal epilepsy (see Section 3). Some TMS/EEG reports suggest that cortical excitability could increase with the time spent awake (Civardi et al., 2001; Kreuzer et al., 2011; Scalise et al., 2006), and decrease after sleep (Huber et al., 2013). This phenomenon is probably enhanced in patients with epilepsy during wakefulness after SD.

This hypothesis is in line with a major explanation of the sleep-related neuronal plasticity. The “synaptic downscaling” or “synaptic homeostatic hypothesis” by Tononi and Cirelli suggests that sleep is the price paid by the brain for plasticity (Tononi and Cirelli, 2014, 2006). According to this hypothesis, during wakefulness, external and environmental stimuli lead to a strengthening of connections throughout the brain. This increases the cellular needs for energy and supplies and the cortical excitability, mainly in the neocortex. Slow-wave activity during NREM sleep would reduce and downscale synaptic strength, avoiding the saturation of neural plasticity, and thus leading to a decreased cortical excitability at the beginning of the subsequent wakefulness. The previously mentioned observations (Badawy et al., 2006; Del Felice et al., 2011) suggest that this phenomenon may be enhanced in patients with epilepsy.

6.3. Epileptiform discharges in SD EEG: the role of sleep instability

In general, epileptiform discharges seem to be enhanced by sleep instability and slow-wave activity. Several paradigms have been developed to evaluate sleep stability and the so-called “sleep microstructure”, as compared with the conventional macrostructural sleep parameters (Iber et al., 2007; Rechtschaffen and Kales, 1968). The most known microstructural phenomenon is the cyclic alternating pattern (CAP), first described in Terzano et al. (1985). CAP is a spontaneous and physiologic rhythm, detectable during NREM sleep, which contributes to the dynamic organization of sleep. It is characterized by very slow EEG oscillations, which are believed to correspond to periods of cyclic activation and deactivation. This infra-slow oscillation is composed of an EEG

transient (phase A of the cycle) separated by intervals of background activity (phase B of the cycle) with a periodicity of 20–40 s. Three main patterns of CAP A phase have been described: subtype A1, characterized by EEG synchronized slow waves; subtype A3, similar to an arousal according to Iber et al. (2007); and subtype A2, a combination of both slow and fast rhythms. The hierarchical activation from slower EEG patterns (moderate autonomic activation without sleep disruption) to faster EEG patterns (robust activation associated with visible sleep fragmentation) can have different meanings. In fact, A1 subtypes are associated with SWS and sleep continuity; A2 and A3 are related to the initiation of REM sleep and relative arousability. The CAP time to NREM sleep time ratio, known as CAP rate, has been reported to be a physiologic marker of sleep instability (Parrino et al., 2012, 2006; Terzano et al., 2001).

CAP modulates and is modulated by many different pathologic phenomena, including sleep apneas, periodic limb movements during sleep, and also seizures and epileptic abnormalities. In fact, seizures seem to cluster during NREM sleep, especially during CAP phases, compared with REM sleep and non-CAP sleep, and to prevail in A phases over B phases (Parrino et al., 2000; Manni et al., 2005). Moreover, the increased CAP rate during the sleep period following a nocturnal seizure suggests that sleep instability might be induced by nocturnal partial seizures, facilitating the occurrence of other events. With regard to IEDs, IGE patients presented more IEDs during CAP sequences than during non-CAP sleep, and 93% of these abnormalities were found in CAP A phases (Halász et al., 2002b). Finally, CAP influences both the occurrence and the generalization of focal abnormalities (Terzaghi et al., 2008, 2007), with the exception of benign childhood epilepsy with centrotemporal spikes. A different neuronal circuit is possibly involved in the latter epilepsy syndrome (Halász, 2013; Parrino et al., 2012).

In general, phases characterized by EEG synchronization and slow waves, such as the entire length of subtypes A1 during the first two sleep cycles, and the initial portions of A2 and A3 subtypes, are more frequently related to IEDs (Halász et al., 2013, 2002b; Parrino et al., 2006). Given the well-established role of sleep instability in inducing IEDs, it seems important to consider the effects of SD on recovery sleep and particularly on CAP parameters. Unfortunately, there are no studies on changes in sleep stability and sleep structure after SD in patients with epilepsy in the literature, and only a few papers on healthy subjects considered these issues (De Gennaro et al., 2002; Parrino et al., 1993; Poryazova et al., 2011; Sforza et al., 2004). The protocols used by these authors are also very different. Duration of SD ranged from 24 h in Parrino et al. (1993) to 64 h in Sforza et al. (2004), whereas Poryazova et al. (2011) adopted a partial SD protocol for several patients. Moreover, a different evaluation of sleep instability and microstructure was applied in the paper by Sforza et al. (2004). Two studies allowed for recovery sleep during the following morning (Parrino et al., 2012; Poryazova et al., 2011), while three postponed it to the subsequent night, thus achieving an SD duration of at least 36 h (De Gennaro et al., 2002; Parrino et al., 1993; Sforza et al., 2004). This difference in the circadian phase of the recovery sleep could lead to a different sleep organization, since both macrostructure, especially REM sleep (Borbély, 1982), and CAP (Terzano et al., 2005) have a homeostatic and a circadian regulation.

In addition, the experimental data appear to be inconsistent. Nocturnal recovery sleep was characterized by increased slow-wave activity and sleep efficiency, whereas total REM time was probably not influenced (De Gennaro et al., 2002). During recovery sleep, a reduced total sleep time occurred without any major changes in the other parameters (Parrino et al., 2012; Poryazova et al., 2011). With respect to the microstructure, nocturnal recovery sleep led to reduced instability and an inhibitory effect on arousal and microarousal responses (Sforza et al., 2004). CAP rate (particularly A3 subtypes) was reduced, since sleep-promoting factors usually increase arousal thresholds (De Gennaro et al., 2002; Parrino et al., 1993). The American Academy of Sleep Medicine (AASM) arousals and other forms of sleep transients were also reduced in frequency (Sforza et al., 2004). On the other hand, recovery sleep in the morning resulted in increased CAP time and CAP rate in a study of healthy young subjects by Parrino et al. (1993). These results have not been confirmed in the successive paper by Poryazova and colleagues, who recruited ten healthy subjects, and allowed them to sleep in the morning after partial (4 h) or total SD. A reduction in CAP parameters was observed, including CAP rate, CAP time, CAP index, CAP cycles, A1 index, and A3 cycles (Poryazova et al., 2011).

Taken together, these results support an influence of SD on the microstructure of sleep. If confirmed, the increased CAP parameters during morning recovery sleep, reported by Parrino and colleagues, could partially explain the tendency of SD EEG to disclose IEDs in the first hours of the morning. In this circumstance, the homeostatic and circadian factors act in opposite directions, promoting and opposing sleep stability, respectively.

It must be emphasized again that the modifications of the recovery sleep in epilepsy patients, which could differ from conditions in healthy subjects, have not yet been investigated.

7. Conclusions and future perspectives

The main goal of our review was to underscore the majority of the current uncertainties regarding both the execution and the interpretation of SD EEG protocols in epilepsy. The most immediate consideration emerging from this analysis is that we urgently need to formulate a set of standardized international guidelines for the execution protocol of SD EEG. In fact, only minimal requirements for this type of examination have been provided up to now in a single ILAE official report (Flink et al., 2002). In our opinion, this step is mandatory to allow for the comparison and pooling of data obtained from different centers worldwide, which currently is impractical. Presumably, such guidelines would be based on consensus statements of experts, given the lack of sufficiently robust and comparative data in favor of a specific protocol. The “ideal” method, however, should consist of periods of SD and EEG recording long enough to maximize IED occurrence, and as short as possible, to be acceptable for the majority of the patients and feasible in most centers. In many studies on adults, the authors induced at least 24 h of SD before recording the EEG, while partial SD protocols have mainly been tested in the last 10–15 years (Table 1). From the analysis of the literature, we observed that relatively short EEGs after partial SD seem to provide a diagnostic yield which is similar to that obtained after 24 h of SD and a longer EEG.

Among these short protocols, the one we have been empirically using for years in our Epilepsy Center, namely a partial SD lasting 6 h, followed by a 150-minute EEG recording, was recently verified as having good specificity and sensitivity (Giorgi et al., 2013). Therefore, we suggest that our protocol might represent one of the options to fulfill the above-mentioned requirements for an “ideal” SD EEG method.

Defining an accepted standard for SD EEG protocols is also mandatory to fully explore the role of SD EEG itself. Correlation analyses, possibly involving hundreds of patients, need to be performed, to pinpoint the population(s) of patients who would most benefit from such a method. Most clinical/instrumental data, necessary to carry out these correlations, are nowadays available worldwide, even in non-specialized facilities: a 1.5-T MRI scan is now obtained for most epilepsy patients, as well as basal EEG recordings, laboratory tests, and detailed clinical/anamnestic information.

In our opinion, such multicenter analyses, pooling data coming from hundreds of cases, would be the only means to retrospectively: (1) formulate definitive conclusions about the specificity of SD EEG, which is the main requisite expected from a diagnostic technique; and (2) make correlations between the IED yield and the putative etiologic, morphologic and topographic features of the epileptic lesions. As we underscore in this literature review, neither of these two aspects have been clarified thus far.

Moreover, from a purely clinical point of view, a uniform and widely accepted SD EEG method is required, not only for retrospective analyses, but also to design prospective multicenter studies with large patient numbers. In particular, in our view, there is a strong need for at least: (1) a prospective study evaluating the prognostic role of the lack of IEDs in SD EEG toward the recurrence of seizures in patients with a normal basal EEG after a single suspected epileptic seizure; and (2) a prospective study addressing the prognostic role of SD EEG (either normal or with specific IEDs) toward the recurrence of seizures after discontinuing AEDs in different subtypes of epilepsy.

Finally, there are still many unresolved issues about the pathophysiology of the effects of SD on EEG features and seizure recurrence in epilepsy, which we tried to emphasize in Sections 3 and 6. Among the variety of research topics worthy of exploration, it appears particularly interesting to address the differential role of natural sleep versus SD-induced sleep in increasing the IEDs yield. In this regard, such an analysis should take into account different types of epilepsy, since sleep CAP variables influence IEDs differently in various epileptic syndromes (Parrino et al., 2012), and circadian rhythms deeply influence CAP variables. It would be interesting to compare putative differences in CAP parameters between nocturnal and post-SD sleep in various syndromes, and to evaluate if these differences would parallel discrepancies in the relative occurrence of IEDs.

8. Literature search strategies and selection criteria

References for this review were detected via PubMed searches of original research contributions published between September, 1965 and June, 2013, using the terms “epilepsy”, “EEG”, “sleep” and “deprivation”. Additional items were individually sought for on PubMed, after being identified among the references of other papers. Review articles were included only if original previously unpublished information about the topic was also contained. Only contributions published in peer-reviewed journals and written in English were taken into consideration.

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